Psychoneuroendocrinology (2014) 46, 14—22

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Chronic stress increases vulnerability to diet-related abdominal fat, oxidative stress, and metabolic risk

Kirstin Aschbacher [a,b,*], Sarah Kornfeld [c], Martin Picard [d], Eli Puterman [a], Peter J. Havel [e], Kimber Stanhope [e], Robert H. Lustig [f,g], Elissa Epel [a,**]

[a] Department of Psychiatry, University of California, San Francisco, CA, United States
[b] The Institute for Integrative Health, Baltimore, MD, United States
[c] California School of Professional Psychology, Alliant International University, San Francisco, CA, United States
[d] Center for Mitochondrial and Epigenomic Medicine, Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA, United States
[e] Department of Molecular Biosciences and Nutrition, University of California, Davis, CA, United States
[f] Department of Pediatrics, University of California, San Francisco, CA, United States
[g] Institute for Health Policy Studies, University of California, San Francisco, CA, United States

Received 16 October 2013; received in revised form 5 March 2014; accepted 2 April 2014

KEYWORDS
Psychological stress;
Obesity;
Abdominal adiposity;
Metabolic syndrome;
Pre-diabetes

Summary
Background: In preclinical studies, the combination of chronic stress and a high sugar/fat diet is a more potent driver of visceral adiposity than diet alone, a process mediated by peripheral neuropeptide Y (NPY).
Methods: In a human model of chronic stress, we investigated whether the *synergistic combination* of highly palatable foods (HPF; high sugar/fat) and stress was associated with elevated metabolic risk. Using a case-control design, we compared 33 post-menopausal caregivers (the chronic stress group) to 28 age-matched low-stress control women on reported HPF consumption (modified Block Food Frequency Questionnaire), waistline circumference, truncal fat ultrasound, and insulin sensitivity using a 3-h oral glucose tolerance test. A fasting blood draw was assayed for plasma NPY and oxidative stress markers (8-hydroxyguanosine and F2-Isoprostanes).

* Corresponding author at: Department of Psychiatry, 3333 California Street, Suite 465, San Francisco, CA 94143-0848, United States. Tel.: +1 415 502 7908; fax: +1 415 476 7744.
** Corresponding author at: Department of Psychiatry, 3333 California Street, Suite 465, San Francisco, CA 94143-0848, United States. Tel.: +1 415 476 7648; fax: +1 415 476 7744.
E-mail addresses: kirstin.aschbacher@ucsf.edu (K. Aschbacher), EEpel@lppi.ucsf.edu (E. Epel).

http://dx.doi.org/10.1016/j.psyneuen.2014.04.003

Results: Among chronically stressed women only, greater HPF consumption was associated with greater abdominal adiposity, oxidative stress, and insulin resistance at baseline (all p's $\leq .01$). Furthermore, plasma NPY was significantly elevated in chronically stressed women ($p < .01$), and the association of HPF with abdominal adiposity was stronger among women with high versus low NPY. There were no significant predictions of change over 1-year, likely due to high stability (little change) in the primary outcomes over this period.
Discussion: Chronic stress is associated with enhanced vulnerability to diet-related metabolic risk (abdominal adiposity, insulin resistance, and oxidative stress). Stress-induced peripheral NPY may play a mechanistic role.

1. Introduction

Metabolic syndrome has reached epidemic proportions, affecting 20—30% of adults worldwide (Grundy, 2008). The implications for the future burden of chronic disease are grave, as metabolic syndrome doubles the risk of cardiovascular disease and increases the risk for type 2 diabetes by five-fold (Grundy, 2008). Although metabolic syndrome is defined as a cluster of medical conditions, abdominal adiposity and insulin resistance are core features, even among those of normal weight (Abbasi et al., 2004; Voulgari et al., 2011). Chronic psychological stress is an emerging risk factor that prospectively predicts metabolic syndrome (Pyykkonen et al., 2010), abdominal fat (Marniemi et al., 2002), and obesity (Brunner et al., 2007). Furthermore, stress-reduction can improve glycemic control in type 2 diabetics (Ismail et al., 2004). Yet, stress reduction has remained essentially an afterthought within the Western medical model, representing a lost opportunity to improve prevention and management.

Stress may promote overeating and physical inactivity, thereby contributing to metabolic risk (Epel et al., 2004a). In addition, there appears to be another important, but underexplored, physiological pathway. Preclinical studies find that chronic stress activates peripheral mechanisms within adipose tissue, which augment the adverse effects of sugar and fat on visceral tissue accumulation (Kuo et al., 2007). In mice fed a high fat/high sugar diet, those mice exposed to chronic stress developed visceral adiposity and metabolic syndrome at a considerably faster rate than their non-stressed counterparts (Kuo et al., 2007). A key biological mechanism for this synergistic interaction is the peripheral action of neuropeptide Y (NPY), released from sympathetic nerve terminals innervating visceral adipose tissue, which stimulates adipocyte growth and rapid expansion of visceral fat mass in response to stress (Kuo et al., 2007).

Excess intake of fat and sugar leads to oversupply of energy substrate (Picard and Turnbull, 2013), which increases the production of reactive oxygen species (ROS) by mitochondria and causes oxidative stress (Anderson et al., 2009). One rodent study has shown that the combination of chronic stress and a high fat/high sugar diet led to greater oxidative stress markers of fatty liver disease (Fu et al., 2010). Elevated markers of oxidative stress are associated with human obesity (Keaney et al., 2003), diabetes (Keaney et al., 2003), and cardiovascular mortality (Roest et al., 2008). Further, 8-hydroxyguanosine (8-oxoG), a marker of RNA oxidation, prospectively predicts long-term mortality among patients with diabetes (Broedbaek et al., 2011). Chronic psychological stress (e.g., caring for a spouse with dementia) has also been associated with heightened levels of both 8-oxoG and the oxidative byproduct F2-Isoprostanes (Epel et al., 2004b; Aschbacher et al., 2013). In turn, oxidative stress can induce insulin resistance (Ceriello and Motz, 2004; Hoehn et al., 2009), fomenting the development of metabolic syndrome (Bremer et al., 2012). However, as yet, no study has assessed the synergistic effects of psychological stress and diet on oxidative stress, insulin resistance and adiposity in humans.

The current study utilized a dementia caregiving model of chronic stress exposure among post-menopausal women and age-matched, non-caregiving low-stress control women in a case-control design. We hypothesized that the synergistic combination of exposure to chronic stress (defined as being a caregiver) and greater highly palatable food (HPF) consumption would be associated with significantly higher waistline circumference and truncal fat (abdominal adiposity), markers of oxidative damage and insulin resistance. These relationships were examined both cross-sectionally at baseline and prospectively over 1 year. In addition, we hypothesized that the chronic stress group would have higher NPY levels relative to low-stress controls, supporting the peripheral mechanism of sympathetic innervation of adipocytes established in rodent models.

2. Methods

2.1. Participants

Sixty-three non-smoking, post-menopausal women participated in a larger study of chronic stress, metabolism, and cellular aging, as described previously (Epel et al., 2010). Women 50—80 years old were recruited from within the larger San Francisco Bay area using flyers, and community advertisements in newspapers, online and on radio stations. Data for HPF were not available for two women, precluding their inclusion in this investigation. Of the remaining 61 women, the chronic stress group (CS) consisted of 33 women providing care for a spouse or parent with dementia (average years of care = 4.7; range: 0.5—16.5 years). Antidepressant use was permitted among CS women, because excluding it would have biased the sample toward highly resilient individuals, whereas the overarching study sought to understand